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EXAMINER	
ART UNIT	PAPER NUMBER
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DATE MAILED: 12/02/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11/1/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-35 are pending in the application.
   Of the above, claims 18-24 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-17, 25-35 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

This application should be reviewed for errors.

Applicant's election without traverse of Group I, claims 1-17 and 25-35 in Paper No. 5 is acknowledged.

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-17 and 25-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of copending application serial no. 08/010,829 in view of Cepko (Ann. Rev. Neurosci. 1989). Cepko discloses genetic modification of neural cells and therefore at the time the claimed invention was made, genetic modification of the neural cells was an obvious variation of any neural cell.

This is a provisional obviousness-type double patenting rejection.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Claims 1-17 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. Applicants' invention appears to be hypothetical in nature since evidence has not been presented to show that the invention works as claimed. The claims have been interpreted as being

drawn to a method of remyelination in vivo and Applicants have failed to present evidence showing that the claimed methods would in fact result in remyelinated axons.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and for failing to teach one of ordinary skill how to make and/or use the invention i.e., failing to provide an enabling disclosure. Applicants have described the methods for remyelination of neurons but have failed to disclose that the methods described would result in the claimed effect, which is the remyelination of axons. Applicants have failed to provide evidence in the form of experimental results indicating that the claimed methods give the claimed results. In view of the lack of experimental evidence and in view of the lack of results in the art teaching remyelination via transplantation of cells, it is not apparent that the invention works as claimed.

Regarding claim 1, the "associating" must be limited to the type of injection and the site of injection since, lacking evidence to the contrary, many methods of "associating" cell types are known. Note that the claims have been interpreted as being drawn to in vivo applications.

Claim 1-17 and 35 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word

"associating" is vague and unclear since the type of association is not apparent.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims 25-28, 30-34 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Hunter et al. Regarding claim 25, Hunter discloses producing glial cells comprising isolating neural stem cells from a donor (Abstract). Hunter discloses proliferating the isolated neural stem cells in a culture medium containing B104 CM, conditioned medium containing growth factors, to produce precursor cells (Abstract, lines 2-3). Hunter discloses differentiating the precursor cells in a second culture medium which is substantially free of said growth factor to obtain glial cells, page 239, column 1, top paragraph. Note that a culture medium containing 33% B104 CM is considered to be substantially free of the growth factor.

Regarding claim 26, Hunter discloses use of serum to culture the cells in Table V.

Regarding claims 27 and 28, Hunter discloses that glial progenitors give rise to oligodendrocytes and astrocytes; therefore astrocytes and oligodendrocytes are glial cells.

Regarding claim 30, Hunter discloses use of aggregates, also known as neurospheres (See materials and methods).

Regarding claims 31-34, Hunter discloses production of astrocytes, oligodendrocytes, precursor cells and glial cells for reasons as stated above.

Thus, the reference anticipates the claims.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 29 is rejected under 35 U.S.C. 103 as being unpatentable over Hunter et al as applied to claims 25-28 and 30-35 above, and further in view of Morrison et al. Claims 25-28 and 30-35 were rejected under 35 U.S.C. 102(b) for reasons as stated above. Morrison discloses that EGF stimulates the proliferation and differentiation of glial cells. It would have been obvious to one of ordinary skill to add EGF to the culture method of Hunter in order to obtain differentiated glial cells since glial cells are known to differentiate into oligodendrocytes and astrocytes (Hunter). One of

ordinary skill would have been motivated to use EGF in the culture method of Hunter in order to obtain large numbers of oligodendrocyte precursors in order to produce a greater number of oligodendrocytes.

Accordingly, the modification of the method of Hunter by adding EGF as suggested by Morrison in order to obtain a method of obtaining glial cells was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1, 3-6 and 35 are rejected under 35 U.S.C. 103 as being unpatentable over Boyles et al taken with Hunter et al , Gage et al and Masters et al. Boyles discloses that both astrocytes and oligodendrocytes are involved in the remyelination process of denervated axons since Boyles discloses that apoD, a lipid involved in the remyelination process, is produced by astrocytes and oligodendrocytes in the central nervous system. Boyles differs from the claims in that the reference fails to disclose transplantation of cultured precursor cells to the demyelinated axon to effect remyelination. However, the secondary references, Hunter, Gage and Masters, cure the deficiency. Masters discloses that oligodendrocytes and astrocytes are derived from a common progenitor and that oligodendrocytes have been shown to play a pivotal role in the myelination process (page 116, second paragraph). Hunter discloses that bipotential glial progenitors give rise to oligodendrocytes and type 2 astrocytes, that live conditioning cells (the B104 CNS neuronal cell line) need to be present to increase production of progenitors (page 235, column 1, first paragraph). Hunter further discloses the method of culturing oligodendrocytes, astrocytes and precursor cells. Gage discloses transplantation of cells to the brain and that the core of most therapeutic approaches is the objective of replacing or reactivating a specific

chemical function in the brain that has been lost as a consequence of disease or damage (column 1, lines 45-65).

Thus, it would have been obvious to one of ordinary skill to add the isolated precursor cells, cultured to produce oligodendrocytes and astrocytes, to the crushed nerves (demyelinated) of Boyles in order to effect remyelination. Boyles teaches that astrocytes and oligodendrocytes produce the lipid apoD necessary for the remyelination process. Therefore, it would have been obvious to one of ordinary skill to transplant the precursor cells, capable of differentiating into astrocytes and oligodendrocytes, to the area of injury in order to produce apoD and thereby facilitate the injury repair process. Boyles provides the motivation to combine the references on page 17812, column 2, last paragraph, wherein it is stated "The function of apoD in neural tissue is unknown. However, the massive accumulation of apoD during nerve regeneration, coupled with its apparent production by the glial or supporting cells of the normal central and peripheral nervous systems, suggests that apoD, like apoE, plays a key role in both normal and regenerating neural tissue".

Regarding claim 1, Hunter discloses culture methods for preparing oligodendrocyte precursor cells (Summary). Hunter further discloses proliferating the isolated neural stem cells in a culture medium containing a growth factor since Hunter discloses use of B104CM conditioned medium, produced by the B104 cells. Hunter discloses that the conditioned medium from the B104 cell line increases production of the progenitor cells and therefore teaches proliferation of precursor cells.

Regarding claims 3, 5 and 6, Gage discloses the transplantation of cells into the human brain. It would have been obvious to one of ordinary skill to use the demyelinated axons of the recipient for transplantation in order to avoid a tissue rejection since Gage discloses that the brain is not a totally an immunologically privileged site.

Regarding claim 4, Hunter discloses use of aggregates of cells, also known as neurospheres (page 236, column 2, second full paragraph).

Regarding claim 35, the combination of references of renders obvious the claimed invention since Boyles teaches that oligodendrocytes and astrocytes are necessary for the remyelination of neurons, and Gage discloses the transplantation of cells into the CNS in order to treat a CNS injury. It would have been obvious to transplant oligodendrocytes and astrocytes into a site of demyelination in order to effect remyelination.

Accordingly, the modification of the method of Boyles by using a precursor cell population as suggested by Hunter, Masters and Gage in order to obtain a method of remyelinating neurons was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 2 is rejected under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters and Gage as applied to claims 1, 3-6 and 35 above, and further in view of Morrison et al. Claims 1, 3-6 and 35 were rejected under 35 U.S.C. 103 for reasons as stated above. Morrison discloses that EGF stimulates the proliferation and differentiation of glial cells. It would have been obvious to one of ordinary skill to add EGF to the culture method of Hunter in order to obtain differentiated glial cells since glial cells are known to differentiate into oligodendrocytes and astrocytes (Hunter) and oligodendrocytes are known to be pivotal to the process of myelination (Masters).

One of ordinary skill would have been motivated to use EGF in the culture method of Hunter in order to obtain large numbers of

oligodendrocytes in order to optimize the process of remyelination since a greater number of oligodendrocytes would facilitate the remyelination process, lacking evidence to the contrary.

Accordingly, the modification of the method of Boyles, Masters, Hunter and Gage by adding EGF as suggested by Morrison in order to obtain a method of remyelinating neurons was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 7, 8 and 10-17 are rejected under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters and Gage. Boyles discloses that both astrocytes and oligodendrocytes are involved in the remyelination process of denervated exons since Boyles discloses that apoD is produced by astrocytes and oligodendrocytes in the central nervous system. Boyles differs from the claims in that the reference fails to disclose transplantation of cultured oligodendrocytes to the demyelinated axon to effect remyelination. However, the secondary references, Hunter, Gage and Masters, cure the deficiency. Masters discloses that oligodendrocytes and astrocytes are derived from a common progenitor and that oligodendrocytes have been shown to play a pivotal role in the myelination process (page 118, second paragraph). Hunter discloses that bipotential glial progenitors give rise to oligodendrocytes and type 2 astrocytes, that live conditioning cells (the B104 CNS neuronal cell line) need to be present to increase production of progenitors (page 235, column 1, first paragraph). Hunter further discloses the method of culturing oligodendrocytes, astrocytes and precursor cells. Gage discloses transplantation of cells to the brain and that the core of most therapeutic approaches is the objective of replacing or reactivating a specific

chemical function in the brain that has been lost as a consequence of disease or damage (column 1, lines 45-65).

Thus, it would have been obvious to one of ordinary skill to add the cultured oligodendrocytes to the crushed nerves (demyelinated) of Boyles in order to effect remyelination. Boyles teaches that astrocytes and oligodendrocytes produce a lipid, apoD, necessary for the remyelination process. Therefore, it would have been obvious to one of ordinary skill to transplant the oligodendrocytes to the area of injury in order to produce apoD and thereby facilitate the injury repair process. Boyles provides the motivation to combine the references on page 17812, column 2, last paragraph, wherein it is stated "The function of apoD in neural tissue is unknown. However, the massive accumulation of apoD during nerve regeneration, coupled with its apparent production by the glial or supporting cells of the normal central and peripheral nervous systems, suggests that apoD, like apoE, plays a key role in both normal and regenerating neural tissue".

Regarding claim 7, Hunter discloses isolation of neural stem cells and proliferating the isolated neural stem cells in a first culture medium containing a growth factor, B104 CM, to proliferate precursor cells (material and methods) and figure 3, figure legend. Note that oligodendrocyte precursor cells are A2B5+/GalC-. Hunter further discloses removal of the progenitor cells from the first culture medium and differentiating the precursor cells in a second medium substantially free of the growth factor since Hunter discloses subsequent growth of progenitors under culture conditions containing 33% ACM (astrocyte condition medium). Culture medium containing 33% ACM is seen to be substantially free of the growth factor in B104 CM, lacking evidence to the contrary.

Regarding claim 8, Hunter discloses the use of serum when evaluating the potential of cells to develop into progenitor cells (Table V, page 242).

Regarding claims 10 and 11, Hunter discloses that type 1 astrocytes produce PDGF (page 241, column 1). It would have been obvious to one of ordinary skill to add PDGF to the culture medium in order to stimulate the production of oligodendrocyte precursor cells. Indeed, Hunter discloses adding PDGF to the culture to achieve does-dependent increases in the number of oligodendrocyte precursor cells (page 241, column 1). In addition the cell population used by Hunter naturally contains some type 1 astrocytes.

Regarding claims 12 and 13, since type 1 astrocytes are known to produce PDGF and PDGF is known to stimulate production of oligodendrocyte precursors, it would have been obvious to one of ordinary skill to add either type 1 astrocytes or PDGF or both to the oligodendrocytes transplanted into the site of injury in order to facilitate the process of remyelination since Masters discloses that oligodendrocytes are central to the process of remyelination.

Regarding claim 14, Hunter discloses that the precursors are in neurospheres on page 239, wherein the enriched population contained some cells differentiated into oligodendrocytes but that most mature oligodendrocytes remained adherent.

Regarding claims 15-17, Gage discloses transplantation of cells to treat diseases of the CNS.

Accordingly, the modification of the method of Boyles by using an oligodendrocyte cell population as suggested by Hunter, Masters and Gage in order to obtain a method of remyelinating neurons was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as

evidenced by the references, especially in the absence of evidence to the contrary.

Claim 9 is rejected under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters and Gage as applied to claims 7, 8 and 10-17 above, and further in view of Morrison et al. Claims 7, 8 and 10-17 were rejected under 35 U.S.C. 103 for reasons as stated above. Morrison discloses that EGF stimulates the proliferation and differentiation of glial cells. It would have been obvious to one of ordinary skill to add EGF to the culture method of Hunter in order to obtain differentiated glial cells since glial cells are known to differentiate into oligodendrocytes and astrocytes (Hunter) and oligodendrocytes are known to be pivotal to the process of myelination (Masters).

One of ordinary skill would have been motivated to use EGF in the culture method of Hunter in order to obtain large numbers of oligodendrocytes in order to optimize the process of remyelination since a greater number of oligodendrocytes would facilitate the remyelination process, lacking evidence to the contrary.

Accordingly, the modification of the method of Boyles, Masters, Hunter and Gage by adding EGF as suggested by Morrison in order to obtain a method of remyelinating neurons was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax

center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800
12/1/93